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09/770,562	01/26/2001	William J. Curatolo	PC9674AJTJ	8513

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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/770,562	Applicant(s) CURATOLO ET AL.	
	Examiner Blessing M. Fubara	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,4-7,10,11,13,15,17,22-39,41-43,45 and 47 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,4-7,10,11,13,15,17,22-27,41-43,45 and 47 is/are rejected.

7)☒ Claim(s) 28-37 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4-7, 10, 11, 13, 15, 17, 22-39, 41-43, 45 and 47 remain in the application.

Prosecution Reopened

1. Prosecution on the merits of this application is reopened on claims 1, 4-7, 10, 11, 13, 15, 17, 22-39, 41-43, 45 and 47 considered unpatentable for the reasons indicated below:

Claim Rejections - 35 USC § 102

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1, 4-7, 10, 11, 13, 15, 17, 22, 27, 39, 41-43, 45 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamaguchi et al. (English Translation of Yakuzaigaku 53(4): 221-228, 1993).

Yamaguchi studies the solubility of solid dispersions of 4-O-(4-methoxyphenyl)acetyltylosin (MAT) in carboxymethylethylcellulose (CMEC) or hydroxypropylmethylcellulose acetate succinate (HPMCAS or AQOAT$^{(R)}$), and using the solid dispersions an increase of AUC and Cmax of greater than 2.5 fold was observed achieved (abstract). Yamaguchi prepares solid dispersions of MAT in CMEC, AQOAT or EC (ethylcellulose) by spray drying (item # 2 of page 2); the solubility of crystalline MAT is determined to be 0.002 at pH 6.8 (item 1 of page 4 and Table 1). In Figure 2 and at pH 4.0, Yamaguchi shows solid dispersions of MAT and CMEC or AQOAT in a ratio of 10:1 and concentration of the MAT in a use environment from AQOAT carrier matrix is about 650 μg and the concentration of amorphous MAT without a polymer in a use environment is about 220 μg; the ratio of the MAT from the AQOAT matrix to a control, such as the one without a polymer is

at least greater than 1.5 and specifically about 2.95 (see page 5 and data extrapolated from Figure 2). Although, Yamaguchi exemplifies the dissolution studies with CMEC, the Yamaguchi reference also discloses MAT with AQOAT as is seen in the abstract, pages 2 (last line) and 5, and Figure 2. MAT bulk powder is used in the study in the preparation of the solid dispersion (page 2, item #1) and powder reads on amorphous. Yamaguchi describes oral administration, fed state (i.e. "withholding food from the beagles from the night before the study") and measuring of blood concentration (page 4, item # 7 and page 10, item # 4), which description confers the implication of gastrointestinal tract environment and thus, this aspect of the disclosure reads on gastrointestinal tract use environment. Although, item #4 of page 10, specifically directs the investigation to MAT/CMEC, this particular disclosure is an exemplification of the MAT solid dispersion, and since the abstract and last line of page 2 and then page 5 disclose MAT/AQOAT solid dispersions, page 10, item #4 would apply to the MAT/AQOAT dispersion. The carriers are different but equivalent in the Yamaguchi disclosure and the drug is the same MAT. The teachings of Yamaguchi meet the limitations of the claims.

4. Claims 1, 7, 11, 13, 15, 27, 39, 41-43, 45 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyajima et al. (US 4,983,593).

Miyajima discloses a pharmaceutical composition that comprises 5-(5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)-1,4-dihydro-2,6-dimethyl-4- (3- itrophenyl)-3-pyridine carboxylic acid 2-(phenylmethyl)amino) ethyl ester P-oxide hydrochloride-thanol (NZ-105) and hydroxypropylmethylcellulose acetate succinate (HPMCAS or AQOAT) in a 1:1 ratio (abstract) and column 4, lines 6-8 discloses NZ-105/HPMCAS composition where the amount of the HPMCAS is 1-7 parts by weight per unit of NZ-105. Miyajima's composition further comprises

filers, binders, lubricants and disintegrants (column 4, lines 22-47). Miyajima's composition is formulated as powders, granules, tablets, capsules or pills (column 4, lines 16-21). Powder or particles of NZ-105 and HPMCAS are produced by vacuum drying, spray drying or freeze-drying (column 3, lines 55-60). While nicardipine and nifedipine are disclosed by Miyajima in the background section as well known 1,4-dihydropyridine-type compounds that are poorly soluble in water and can be prepared as amorphous formulations, the nicardipine and nifedipine are different compounds from the compounds recited in instant claims 29, 30, 32, 34 and 36. Instant claim 37 recites nifedipine as a drug.

Examples 1-4 of Miyajima disclose NZ-105/HPMCAS composition where the ratio of the NZ-105 to the HPMCAS is 1:3. Miyajima is silent with respect to the solubility of the drug NZ-105 in a use environment or oral administration or administration to a fasted animal. However, the solubility of the drug is an inherent property of a drug and would appear to be an inherent property of the NZ-105/HPMCAS compositions. It is noted that no specific drug is claimed in the claims in question. Thus, Miyajima meets the limitations of the claims.

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyajima et al. (US 4,983,593).

Miyajima discloses the instant composition that comprises a sparingly water-soluble drug and HPMCAS. Although Miyajima discloses that the composition is preparable as particles, Miyajima fails to disclose particle sizes. It is also noted that there is no demonstration in

applicants' specification that the recited particle sizes provide unusual results. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a pharmaceutical composition comprising NZ-105 and HPMCAS and spray dried to form amorphous dispersed solid particles. One having ordinary skill in the art would have been motivated to prepare particles of a formulation containing NZ-105 and HPMCAS with the expectation that the NZ-105 would be more soluble and in the absence of unexpected result, the particle size recited does not distinguish the instant claims over the prior art.

7. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miyajima et al. (US 4,983,593).

Miyajima discloses the instant composition that comprises a sparingly water-soluble drug and HPMCAS. Although Miyajima in the background section discloses nifedipine as poorly water-soluble drugs, whose solubility can be improved, Miyajima's disclosed composition does not contain nifedipine. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a composition that contains NZ-105 and HPMCAS. One having ordinary skill in the art would have been motivated to prepare a composition that contains nifedipine and HPMCAS according to the suggestion of Miyajima with the expectation of improving the solubility of nifedipine.

8. Claims 28-37 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art does not teach composition comprising HPMCAS and glycogen phosphorylase inhibitors of claims 28-30 or the corticotropic releasing hormone

inhibitors of claims 33-35 or the 5-lipoxygenase inhibitor of claims 31 and 32 or antipsychotic of claims 36 and 37.

9. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is requested in correcting any errors of which applicants may become aware in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 3:30 p.m. (Monday to Friday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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